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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/684,893	10/14/2003	J. Milton Harris	044646/262893	4856

826 7590 01/21/2010

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EXAMINER	
FISHER, ABIGAIL L	
ART UNIT	PAPER NUMBER
1616	

MAIL DATE	DELIVERY MODE
01/21/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/684,893	HARRIS, J. MILTON	
	Examiner	Art Unit	
	ABIGAIL FISHER	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 September 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13,15,16 and 19-27* is/are pending in the application.

4a) Of the above claim(s) *25-27* is/are withdrawn from consideration.

5)☒ Claim(s) *15 and 16* is/are allowed.

6)☒ Claim(s) *1-9,11,19,23 and 24* is/are rejected.

7)☐ Claim(s) *10,12-13, 20-22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/31/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Receipt of Amendments/Remarks filed on September 30 2009 is acknowledged. Claims 14 and 17-18 were/stand cancelled. Claims 1-5, 10, 12, 15-16 and 20-22 were amended. Claims 1-13, 15-16 and 19-27 are pending. Claims 25-27 are withdrawn as being directed to a non-elected invention. Claims 1-13, 15-16 and 19-24 are directed to the elected invention.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 3/31/09 was considered by the examiner.

Allowable Subject Matter

Claims 15-16 are allowed. The following is a statement of reasons for the indication of allowable subject matter: Claim 15 recites a crosslinked polymeric structure that possess a specific structure. This structure was found to be free of the art.

Claim Objections

Claims 10, 12, 13 and 20-22 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1-8, 9, 17-18 and 23-24 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in light of Applicants' arguments filed on 9/30/09.

The additional rejection of claims 1-6, 9-10 and 23-24 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for the following additional reason is **withdrawn** in light of Applicants' amendments filed on 9/30/09.

Modified Rejection Based on amendments in the reply filed on 9/30/09

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 as currently written is vague and indefinite. Claim 11 recites that the R moiety includes glycerol oligomers. The glycerol oligomers are a component that makes up the claimed polymeric structure. Glycerol oligomers are by definition polymers. A glycerol oligomer is a polymer of glycerol. However claim 1 indicates that the polymeric structure comprises PEG polymers in the absence of non-PEG polymers. Therefore, it is unclear how glycerol oligomers can be components of the polymeric structure when non-PEG polymers are expressly excluded from the polymeric structure.

Response to Arguments

Applicants argue that one of skill in the art would readily understand an oligomer to be a chemical structure with a limited number of repeat units whereas polymers are understood to contain more repeat units. It is argued that polymers and oligomers are understood to refer to different materials.

Applicants' arguments filed September 30 2009 have been fully considered but they are not persuasive.

Applicants agree that oligomers have repeat units. Therefore, this supports the notion that oligomers are understood to be polymers. Claim 1 excludes all polymers other than PEG. There is no length requirement for the exclusion. While oligomer and polymer possess different names, an oligomer is a specific type of polymer. The Aldrich

catalog defines oligomer to be a very low molecular weight polymer, ranging form about 2 to twenty monomer units. Therefore, while an oligomer may be a low molecular weight polymer, it is still a polymer.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejection of claims 1-9, 17-18 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jamiolkowski et al. (US Patent No. 5698213)is **withdrawn** in light of Applicant's argument that Jamiolkowski et al. is only available as prior art as of the filing date priority document (US Patent 5607687) and that this document does not teach that the polymer form hydrogels.

Claims 1-9, 19 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et al. (US Patent No. 5648506, cited on PTO Form 1449).

Applicant Claims

Applicant claims a hydrogel crosslinked polymeric structure comprising poly(ethylene glycol) (PEG) polymers in the absence of non-PEG polymers. The PEG polymers have at least some hydrolytically unstable linkages between said PEG polymers that are hydrolysable under hydrolysis conditions, said hydrolysable linkages comprising linkages selected from the group consisting of carboxylate esters, phosphate esters, imines, hydrazones, acetals, orthoesters, and oligonucleotides.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Desai et al. is directed to water-soluble polymer carriers for Drug Delivery. The invention relates to the drug delivery of taxol wherein the drug is chemically bound to a water-soluble polymer or macromolecular carrier that renders the drug water-soluble (column 1, liens 10-20). It is taught that the preparation of reversible PEG-taxol derivative at the 2' and/or 7-position on taxol serves as useful aqueous soluble prodrug. A nonreversible PEG derivative on the 7-position of taxol serves as a useful water-soluble drug analogue (column 2, lines 32-37). In a preferred embodiment, taxol is covalently linked to a PEG carboxylic acid derivative by an esterification at the 2'-position on the taxol side chain (i.e. reaction with taxol alcohol at the 2' position) (column 3, lines 10-12). It is taught that other drugs may be utilized in a similar form of drug delivery (column 4, lines 25-26). It is taught that the purpose of covalently linking a

water-insoluble or poorly water-soluble drug to a water-soluble polymer is to solubilize the drug in water to enable its delivery in a soluble form into the body (column 4, lines 37-40). As exemplified in table 1, peg polymers were attached to taxol via amide linkages (compound 3) or ester linkages (compound 7). PEG was linked to taxol with relatively stable urethane linkages at the 7 position as coupling of PEG with stable linkages at the 2' position would be expected not to have a high biological activity (column 5, lines 35-45). Alternatively PEG could be attached at the 2' position of taxol with hydrolysable ester linkages to release taxol in an active form after delivery of the drug (column 5, liens 59-64). In these examples the number of drug molecules per carrier is restricted to a maximum of two taxol molecules per molecule of PEG and only one taxol per MPEG. In order to increase the number of taxols per carrier molecule, PEGS with multiple arms such as branched molecules or star molecules are utilized (column 6, lines 27-32). One such 'star molecules' in one that has an oligomeric glycerol central core that is ethoxylated and used to initiate polymerization of ethylene oxide and then quenched when the desired molecular weight is achieved (column 7, lines 7-10). Examples 1-4 teach linking taxol to PEG at either the 2, 7 or both linkage sites via either hydrolytically stable urethane linkages or hydrolysable ester linkages. Example 5 is directed to the use of a branched chain or "start' PEG for multiplicity of attachment sites. It is taught that the reactions described in examples 1 through 4 can be utilized to covalently attach drugs to these molecules. Example 7 is directed to a hydrogel containing bound taxol for sustained release drug delivery. It is taught that the derivative is crosslinked.

Ascertainment of the Difference Between Scope the Prior Art and the Claims *(MPEP §2141.012)*

While Desai et al. teach that core of the 'star' molecules with peg arms can be oligomeric glycerol, Desai et al. do not exemplify this star molecule with taxol attached. While Desai et al. teach that taxol can be linked to PEG via hydrolytically unstable ester linkages or hydrolytically stable urethane linkages and suggests both can be utilized, Desai et al. do not exemplify structures with both.

Finding of Prima Facie Obviousness Rational and Motivation (MPEP §2142-2143)

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize both hydrolytically unstable ester linkages and hydrolytically stable urethane linkages in the connection of PEG to taxol. One of ordinary skill in the art would have been motivated to utilize both as Desai et al. teach that taxol can be linked to PEG in either manner and suggests that hydrolytically unstable linkages can provide a releasable form of taxol. Since the linkage of PEG with taxol is designed to enhance the water solubility of the drug for delivery and that the free OH at the 2 position is required for activity it would have been obvious to one of ordinary skill in the art to attach taxol to PEG at the 2 position in order to provide a hydrolysably releasable taxol moiety and to attach taxol to PEG at the 7 position in order to maintain the water solubility of the taxol moiety after delivery as taught by Desai et al.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to utilize a glycerol oligomer as the core for the branching star group of PEG linkages. One of ordinary skill in the art would have been motivated to utilize a

glycerol oligomer as it is specifically taught by Desai et al. as one type of core that can be utilized to attach PEG polymers. Furthermore, it would have been obvious to one of ordinary skill in the art to attach taxol to these PEG star molecules utilizing both ester and urethane linkages as Desai et al. teach that either of these types of linkages can be utilized to attach taxol (or other drugs) to the star molecules.

Regarding the claimed crosslinking, the instant claims indicate that the PEG polymers are crosslinked in the absence of photopolymerization or free-radical polymerization. This limitation is interpreted as a product by process limitation. **Note MPEP 2113 [R-1]** "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). The MPEP also indicates that "the structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979). Therefore, as long as the final product is the same as instantly claimed, the crosslinking does not have to be the same as instantly claimed.

Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

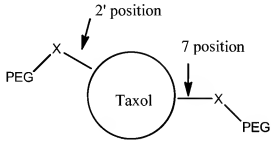
Response to Arguments

Applicants argue that (1) the hydrolytically unstable linkages referred to in the present specification and claims are present in the backbone of the polymeric materials and are included to provide release of the drug and hydrolytic degradation. It is argued that Desai does not contain any mention of hydrolytically unstable linkages between the PEG components. Applicants argue that (2) the polymers of Desai are prepared via free radical polymerization however claim 1 states that the crosslinked polymeric structure is crosslinked in the absence of photopolymerization or free radical polymerization.

Applicants' arguments filed September 30 2009 have been fully considered but they are not persuasive.

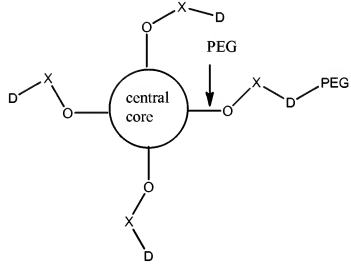
Regarding applicant's first argument, firstly there is no requirement in claim 1 (or any of the other above rejected claims) that the hydrolytically unstable linkages are present in the backbone. Claim 1 requires at least some hydrolytically unstable linkages between said PEG polymers. The open language comprising allows for other components to be present as well. Desai teaches attaching PEG at the 2' and 7 position of taxol. Therefore looking at the following representation (it is noted that the examiner is just using an abbreviation for components rather than drawing everything

out) one can see that the PEG monomers are separated by the hydrolytically unstable linkages.



wherein X is the likage between taxol and PEG

Drawing 1



This is a simialr drawing to that seen in Desai (column 7). Additionally, the D can have PEG attached at the other position (either 2' or 7) depending on whether or not attached to core at 2' or 7.

Drawing 2

Therefore, based on these two drawings (which are interpretations of the teachings of Desai), the PEG containing polymeric structures taught by Desai still render the above rejected claims obvious.

Regarding applicants' second argument, as indicated in the last Office action, the limitation that the PEG polymers are crosslinked in the absence of photopolymerization or free-radical polymerization is interpreted as a product by process limitation. **Note MPEP 2113 [R-1]** "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). The MPEP also indicates that "the structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979). Therefore, as long as the final product is the same as instantly claimed, the crosslinking does not have to be the same as instantly claimed.

Therefore, the rejections are maintained for the above rejected claims.

Conclusion

Claims 1-9, 11, 19 and 23-24 are rejected. Claims 10, 12-13 and 20-22 are objected. Claims 15-16 are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ABIGAIL FISHER whose telephone number is (571)270-3502. The examiner can normally be reached on M-Th 9am-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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